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Stroke Risk in Patients With Reduced Ejection Fraction After Myocardial Infarction Without Atrial Fibrillation

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ABSTRACT

BACKGROUND Stroke can occur after myocardial infarction (MI) in the absence of atrial fibrillation (AF).

OBJECTIVES This study sought to identify risk factors (excluding AF) for the occurrence of stroke and to develop a calibrated and validated stroke risk score in patients with MI and heart failure (HF) and/or systolic dysfunction.

METHODS The datasets included in this pooling initiative were derived from 4 trials: CAPRICORN (Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction), OPTIMAAL (Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan), VALIANT (Valsartan in Acute Myocardial Infarction Trial), and EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study); EPHESUS was used for external validation. A total of 22,904 patients without AF or oral anticoagulation were included in this analysis. The primary outcome was stroke, and death was treated as a "competing risk."

RESULTS During a median follow-up of 1.9 years (interquartile range: 1.3 to 2.7 years), 660 (2.9%) patients had a stroke. These patients were older, more often female, smokers, and hypertensive; they had a higher Killip class; a lower estimated glomerular filtration rate; and a higher proportion of MI, HF, diabetes, and stroke histories. The final stroke risk model retained older age, Killip class 3 or 4, estimated glomerular filtration rate ≤45 ml/min/1.73 m^2, hypertension history, and previous stroke. The models were well calibrated and showed moderate to good discrimination (C-index = 0.67). The observed 3-year event rates increased steeply for each sextile of the stroke risk score (1.8%, 2.9%, 4.1%, 5.6%, 8.3%, and 10.9%, respectively) and were in agreement with the expected event rates.

CONCLUSIONS Readily accessible risk factors associated with the occurrence of stroke were identified and incorporated in an easy-to-use risk score. This score may help in the identification of patients with MI and HF and a high risk for stroke despite their not presenting with AF. (J Am Coll Cardiol 2018;71:727–35) © 2018 the American College of Cardiology Foundation. Published by Elsevier. All rights reserved.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

eGFR = estimated glomerular filtration rate

HF = heart failure

MI = myocardial infarction

OAC = oral anticoagulant agent

Stroke may be potentially devastating for patients and has important impacts on their families, caregivers, and society (1). Stroke can occur after myocardial infarction (MI), thus further complicating MI management and increasing associated death rates (2). The incidence rates of stroke after MI vary between ≈1% and 5% (3-6). The formation of areas of akinesia and/or dyskinesia in the left ventricle after MI may increase the risk for mural thrombi formation and subsequent peripheral thromboembolism and stroke (7). Nonetheless, these reports included patients with atrial fibrillation (AF), which is a major risk factor for stroke (8). Hence, whether MI, akinesia, systolic dysfunction, heart failure (HF), AF, or other factors contribute to the occurrence of stroke in the post-MI setting is difficult to ascertain (9). Consequently, the risk of stroke in post-MI patients but without AF is poorly defined.

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MI complicated by systolic dysfunction and/or HF (but without AF) may create a particularly thrombogenic environment per se, through fulfillment of the Virchow triad (stasis of blood flow, endothelial injury, and hypercoagulability) (10). Therefore analyzing the incidence and risk factors for stroke in a group of patients with "complicated" MI without AF may help identify patients at high risk who could benefit from early intervention (e.g., oral anticoagulation) for stroke prevention.

The high-risk MI initiative provided a unique opportunity to study the occurrence of stroke in patients with "complicated" MI but without AF in >20,000 patients and 600 stroke events. The present study aimed to identify the characteristics of the patients who had a stroke during follow-up and to develop a calibrated and validated stroke risk score in this group of patients.

METHODS

STUDY GROUP. The high-risk MI initiative consists of a previously published cohort of pooled patient data derived from 4 clinical trials (11). Briefly, the main objectives of the project were to provide a comprehensive and statistically robust analysis of long-term clinical outcomes in high-risk survivors of MI. The datasets included in this pooling initiative were as follows: the CAPRICORN (Effect of Carvedilol on Outcome After Myocardial Infarction in Patients With Left Ventricular Dysfunction) trial (12,13); EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) (14,15); OPTIMALL (Optimal Trial in Myocardial Infarction With Angiotensin II Antagonist Losartan) (16,17); and VALIANT (Valsartan in Acute Myocardial Infarction Trial) (18,19). Full details of total enrolled patients, the inclusion and exclusion criteria for each trial, the endpoints, and the results have previously been published (11). Each trial enrolled patients with left ventricular systolic dysfunction, HF, or both between 12 h and 21 days after acute MI. The information included in this pooled database did not include the treatment randomization assignments for each trial.

The respective chairpersons of the steering committees of the 4 trials initiated the pooling project. The studies were all conducted in accordance with the Declaration of Helsinki and were approved by site ethics committees. All participants gave written informed consent to participate in the studies.

For the present analysis, we selected patients without a history of AF or without AF present at randomization electrocardiography or those not treated with an oral anticoagulant agent (OAC).

OUTCOMES. The primary outcome was stroke. Stroke was consistently defined as a focal neurologic deficit lasting >24 h or resulting in death that was presumed to be related to stroke. All-cause death was considered the competing risk event.

Endpoints were independently adjudicated in the respective trials.

STATISTICAL METHODS. Continuous variables were expressed as mean ± SD and categorical variables as frequencies and proportions. For comparison of means and proportions, the Student's *t*-test and the chi-square test were used, respectively.

Novartis, Novo Nordisk, Relypsa, Sanofi, Teva, and Thrasos; has received stock options from DalCor; and has received a share, which has been irrevocably assigned to charity, of a patent awarded to Brigham & Women's Hospital and licensed by Novartis. Dr. Pitt has been a consultant for Bayer, AstraZeneca, Sanofi, Relypsa, Vifor, scPharmaceuticals, Stealth Peptides, Tricida, Sarfez Pharmaceuticals, and KDP Pharmaceuticals; and has received stock options from Relypsa and scPharmaceuticals. Dr. Zannad has received fees for serving on the board of Boston Scientific; has received consulting fees from Novartis, Takeda, AstraZeneca, Boehringer Ingelheim, GE Healthcare, Relypsa, Servier, Boston Scientific, Bayer, Johnson & Johnson, and Resmed; has received speaker fees from Pfizer and AstraZeneca; has been Janssen steering committee chair; and is a co-founder of CardioRenal. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Time-to-event analysis was conducted using a competing risk model as described by Fine and Gray (20), with stroke as outcome event and death as competing risk. Log-linearity was checked by testing the functional forms of the covariable by the Kolmogorov-type supremum test and by visual inspection by plotting the beta estimates versus the mean across deciles. Covariables were entered in the multivariable model in a stepwise regression analysis with the p value to enter and stay in the model set to $p = 0.15$ and $p = 0.05$, respectively. Covariables considered to be of potential prognostic impact were age, sex, body mass index, smoking status, systolic blood pressure, heart rate, Killip class, estimated glomerular filtration rate (eGFR, calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [21]), previous MI, history of HF, peripheral artery disease, hypertension, diabetes mellitus, previous stroke, and medications (use of angiotensin-converting enzyme inhibitors, beta-blockers, diuretics, statins, and aspirin). These variables had a small proportion of missing values (<10%), and no multiple imputation was performed. We assessed interactions with the *Log* of time, age, sex, systolic blood pressure, and diabetes, but none were significant (all $p > 0.10$).

Discrimination of the competing risk regression model was assessed by calculating the C-statistics. Assessment of the calibration was performed by visually plotting the cumulative incidence of observed versus expected stroke events derived from the competing risk model across sextiles of the predicted risk. Internal validation of the model was performed by bootstrapping (50x), and external validation was performed in the EPHESUS trial dataset.

To create a simple integer risk score, continuous variables included in the chosen model were categorized into either 2 or 3 groups by using a combination of established clinical cutpoint and graphic examination of rates across quintiles. To simplify the risk score, integer points were assigned to each prognostic factor on the basis of the log-hazard ratio estimates. The total risk score for each patient was calculated by summing the points across all chosen prognostic variables. From the overall distribution of the risk score we formed 6 categories of risk, containing approximately equal numbers of events. Within each risk category and by treatment group we calculated the number of events, person-years at risk, and the overall event rate. Kaplan-Meier plots were drawn showing the cumulative incidence curves by treatment group and risk category.

All analysis was performed with STATA software version 14 (StataCorp, College Station, Texas). A p value <0.05 was considered statistically significant.

RESULTS

STUDY GROUP CHARACTERISTICS. From the initial 28,771 patients included in the high-risk MI pooled dataset (11), 3,754 were excluded from the analysis because of the presence and/or history of AF, and 2,113 patients were additionally excluded for being prescribed OAC, thereby leaving 22,904 patients included in the current analysis.

The mean age was 64 ± 11 years, and 30% of patients were female. Patients who had a stroke during follow-up were older, more often female, and smokers; they had higher systolic blood pressure; were more often Killip class 3 or 4; had lower eGFR; and had a higher proportion of previous MI events, HF history, hypertension, diabetes, and previous stroke (**Table 1**).

During a median follow-up of 1.9 years (interquartile range: 1.3 to 2.7 years), 660 (2.9%) patients had a stroke. The stroke incidence rate was 4.1 (95% confidence interval [CI]: 3.9 to 4.5) per 1,000 patient-years (**Table 1**).

RISK MODELS. The covariates retained in the final stroke risk model are depicted in **Table 2**. Older age, Killip class 3 or 4, eGFR ≤45 ml/min/1.73 m^2, hypertension history, and previous stroke were independently associated with increased risk of stroke.

The models were well calibrated: a steep gradient in risk by sextiles of predicted risk was observed (**Figures 1 and 2,** Online Table 1), and showed moderate/good discrimination (C-index = 0.67). The integer risk score derived from these covariates ranges from 0 to 11 points (**Table 2**).

The model calibration remained good when patients with previous stroke were excluded from the analysis (Online Table 2).

The external validation was performed in the EPHESUS dataset, also with good calibration and discrimination (**Table 3,** Online Table 3).

EVENT RATES. The 1, 2, and 3-year observed cumulative incidence rates of stroke were 1.3% (95% CI: 1.2% to 1.4%), 1.5% (95% CI: 1.4% to 1.6%), and 1.6% (95% CI: 1.5% to 1.7%), respectively.

The observed 3-year stroke event rates increased steeply for each category of the risk score (1.8%, 2.9%, 4.1%, 5.6%, 8.3%, and 10.9%, respectively) and were in agreement with the expected event rates (**Figure 1,** Online Table 1).

The Online Calculator is a tool to calculate stroke risk prediction in each individual patient (with the

TABLE 1 Characteristics of Patients Without Atrial Fibrillation and With No Oral Anticoagulant Agents

	N	No Stroke (n = 22,244)	Stroke (n = 660)	p Value
Age, yrs	22,904	64.1 ± 11.4	68.7 ± 10.0	<0.0001
Female	22,904	6,570 (29.5)	224 (33.9)	0.015
BMI, kg/m^2	22,368	27.5 ± 4.9	27.2 ± 4.2	0.064
Current smoker	22,882	6,730 (30.3)	244 (37.0)	<0.0001
SBP, mm Hg	22,863	121.8 ± 16.8	125.1 ± 18.6	<0.0001
Heart rate, beats/min	22,850	75.3 ± 12.4	76.0 ± 13.4	0.15
LVEF, %	15,578	34.7 ± 8.8	34.4 ± 9.4	0.60
Killip class 3 or 4	22,819	3,876 (17.5)	162 (24.6)	<0.0001
eGFR, ml/min/1.73 m^2	21,974	71.3 ± 38.8	66.5 ± 31.9	0.002
Hemoglobin, g/l	10,298	133.7 ± 15.9	133.1 ± 14.6	0.55
Sodium, mmol/l	10,550	139.4 ± 3.8	139.1 ± 3.5	0.14
Potassium, mmol/l	10,497	4.3 ± 0.5	4.2 ± 0.5	0.16
Previous MI	22,902	5,537 (24.9)	207 (31.4)	0.0002
CABG	22,904	1,117 (5.0)	31 (4.7)	0.71
PCI	22,904	4,673 (21.0)	82 (12.4)	<0.0001
HF history	22,904	8,215 (36.9)	270 (40.9)	0.037
PAD	22,903	1,694 (7.6)	63 (9.5)	0.066
Hypertension	22,904	11,890 (53.5)	407 (61.7)	<0.0001
Diabetes mellitus	22,904	5,576 (25.1)	202 (30.6)	0.001
COPD	22,904	1,769 (8.0)	56 (8.5)	0.62
Previous stroke	22,904	1,522 (6.8)	115 (17.4)	<0.0001
Aspirin	22,904	19,791 (89.0)	592 (89.7)	0.56
ACE inhibitors/ARBs	18,283	9,951 (55.8)	240 (52.1)	0.11
Beta-blockers	21,282	13,908 (67.4)	391 (61.7)	0.003
Diuretics	22,904	9,415 (42.3)	323 (48.9)	0.0007
Statins	22,904	7,654 (34.4)	167 (25.3)	<0.0001
Stroke	22,904	0 (0.0)	660 (100.0)	<0.0001
ACM	22,904	3,372 (15.2)	281 (42.6)	<0.0001

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ACM = all-cause mortality; ARBs = angiotensin receptor blockers; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

TABLE 2 Multivariate Competing Risk Model for Stroke*

Final Model	HR (95% CI)	Coefficient	p Value	Integer
Age, yrs				
<60	Referent	–	–	
≥60 to 75	1.82 (1.48-2.25)	0.60	<0.001	+2
>75	2.12 (1.65-2.73)	0.75	<0.001	+3
Killip class 3 or 4	1.31 (1.09-1.57)	0.27	0.004	+1
eGFR, ml/min/1.73 m^2				
>60	Referent	–	–	
>45 to 60	0.91 (0.74-1.11)	−0.09	0.37	–
≥30 to ≤45	1.29 (1.02-1.63)	0.26	0.031	+1
Hypertension	1.18 (1.00-1.40)	0.17	0.045	+1
Previous stroke	2.21 (1.78-2.74)	0.80	<0.001	+3

*Model C-index (Harrell's C) = 0.67. Final report after 50x bootstrap.

CI = confidence interval; eGFR = estimated glomerular filtration rate; HR = hazard ratio.

characteristics of those included in the present study).

Event rates in patients with atrial fibrillation. Among the 3,754 patients with AF at baseline, 215 (5.7%) had a stroke during a median follow-up of 1.7 years (interquartile range: 1.0 to 2.4 years). The stroke incidence rate was 9.5 (95% CI: 8.3 to 10.8) per 1,000 patient-years. The cumulative incidence at 1, 2, and 3 years was 2.9% (95% CI: 2.7% to 3.1%), 3.3% (95% CI: 3.0% to 3.6%), and 3.4% (95% CI: 3.1% to 3.7%), respectively.

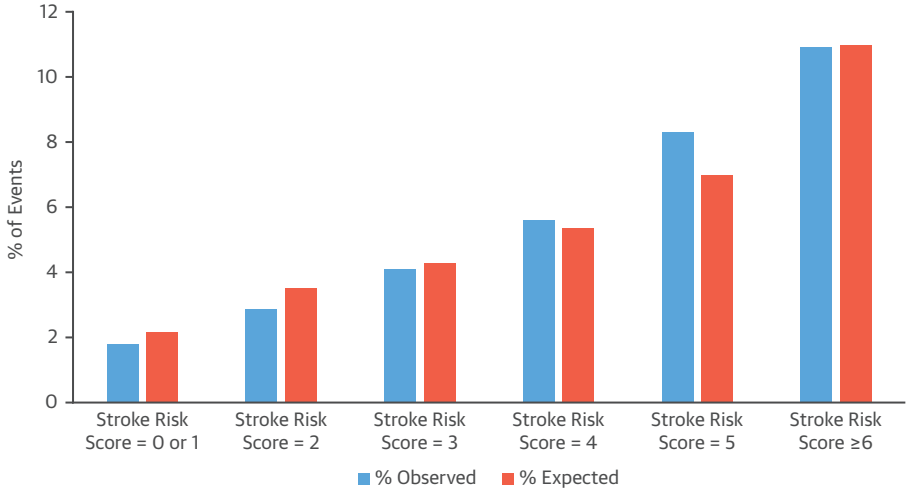
DISCUSSION

Our study identified readily available clinical risk factors associated with stroke in a group of patients with MI complicated by systolic dysfunction and/or HF but without AF (or OAC treatment) (**Central Illustration**). These risk factors were computed in an easy-to-use risk score that provides useful prognostic information to clinicians and may serve to ascertain "risk enhancement strategies" in future trials for stroke prevention in patients with these characteristics. However, practical decisions regarding anticoagulation in this study group warrant prospective and randomized evidence before any such advice is provided.

Overall, post-MI patients with systolic dysfunction but without AF may have a higher risk of stroke than individuals without MI. However, this risk may still vary considerably among MI survivors, and it may be low (<2% at 3 years) for patients in the bottom sextile of our risk score or high (>10%) in patients with several risk factors (e.g., older age, impaired renal function, hypertension, previous stroke, or Killip class 3 or 4) in the top sextile of the risk score.

The overall stroke rate in our pooled data analysis overlapped that reported in other post-MI cohorts. In the Survival and Ventricular Enlargement trial (6) including 2,231 post-MI patients who had left ventricular systolic dysfunction and were followed for ≈42 months, 4.6% (n = 103) had a stroke during the study (1.5% event rate per follow-up year). However, 16% of patients with stroke had AF versus 10% of patients without stroke (p = 0.03). Similarly, older age was also an independent risk factor for stroke. Reports derived from population data show a ≈4% stroke incidence at 1 year post-MI and describe similar independent risk factors for stroke, such as age and previous stroke (5). A meta-analysis (22) reported lower rates of stroke in the post-MI setting (≈1% to 2%), but it also found older age, hypertension, and history of prior stroke (in addition to anterior MI, HF, diabetes, and AF) as independent risk

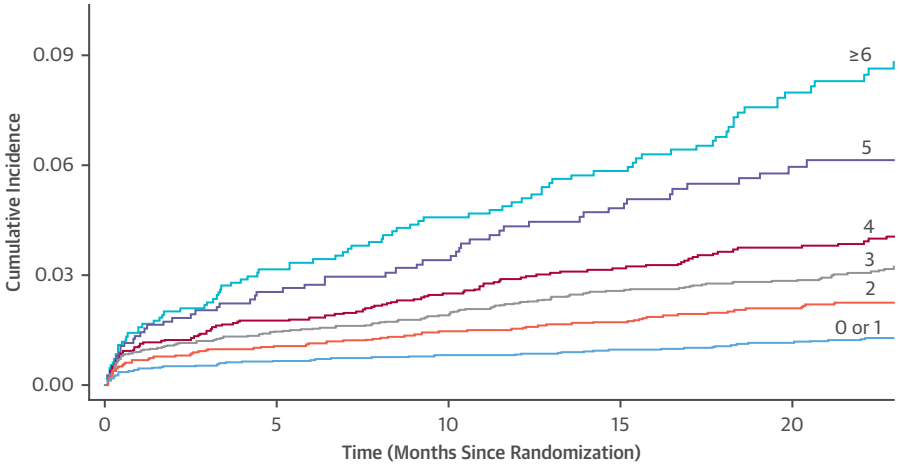
FIGURE 1 Model Calibration Plot: Percentage of Observed Versus Predicted Events at 3 Years by Categories of Stroke Risk Score



The models were well calibrated: a steep gradient in risk by sextiles of predicted risk was observed.

factors for stroke. Although these reports reinforce the external validity of our results, one should notice that the study group included in our pooled dataset is a "high-risk" group (i.e., all patients had MI complicated by systolic dysfunction and/or HF [or diabetes in the EPHESUS trial]), hence it is not surprising that we found higher stroke rates than those reported in "population-derived data." However, when looking at patients with similar characteristics (as in the Survival and Ventricular Enlargement trial), we find

FIGURE 2 Kaplan-Meier Failure Estimates Curve by Stroke Risk Score Categories for the Outcome of Stroke With Death as Competing Risk



Score	Number at risk				
0 or 1	17072	6722	6423	5713	4617
2	23830	3521	3391	3080	2590
3	35354	4839	4574	4066	3337
4	43178	2726	2538	2230	1747
5	51154	935	854	743	563
≥6	61304	1065	966	832	643

Stroke event rates increase by stroke risk score categories.

TABLE 3 External Validation of the Risk Model in the EPHESUS Dataset*

Stroke Risk Score (6 Categories)	n (%)	Events, n	Observed, %	Expected, %
0 or 1	1,789 (35.5)	17	1.5	1.8
2	689 (13.7)	14	3.7	3.0
3	1,217 (24.2)	31	3.8	3.6
4	734 (14.6)	24	4.2	4.1
5	277 (5.5)	12	6.7	5.0
≥6	332 (6.6)	12	7.0	8.2

*C-index of the stroke risk model in the EPHESUS dataset = 0.66.
EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study.

overlapping stroke rates (despite not having patients with AF in our cohort). Although lower left ventricular ejection fraction has been reported as a risk factor for stroke (6), this was not the case in our analysis. This finding may reflect the overall low ejection fraction of our study group, where an ejection fraction <35% was an entry criterion for these trials.

In patients with AF the risk of stroke and also the strategies to avoid stroke are much better developed. Readily accessible risk scores are available for use in clinical practice. For instance the CHA_2DS_2-VASc (congestive HF, hypertension, age ≥75 years [doubled], diabetes, stroke [doubled], vascular disease, age 65 to 74 years, and sex category [female]) score (23) is recommended by the current guidelines, and its use has been extensively validated (24,25) (although the C-index of this score does not exceed 0.6 in most populations [23]). Notwithstanding, in daily practice most patients with AF and a CHA_2DS_2-VASc score of 1 or greater (according to the European Society of Cardiology guidelines) or ≥2 (according to the American Heart Association, American College of Cardiology, and Heart Rhythm Society joint guidelines) should be treated with anticoagulant therapy (unless contraindicated or counterbalanced by a high bleeding risk) (24,25). In the present study group, the CHA_2DS_2-VASc score performed worse for predicting stroke compared with our risk score (C-index = 0.63 for CHA_2DS_2-VASc vs. 0.67 for our score; $p < 0.001$).

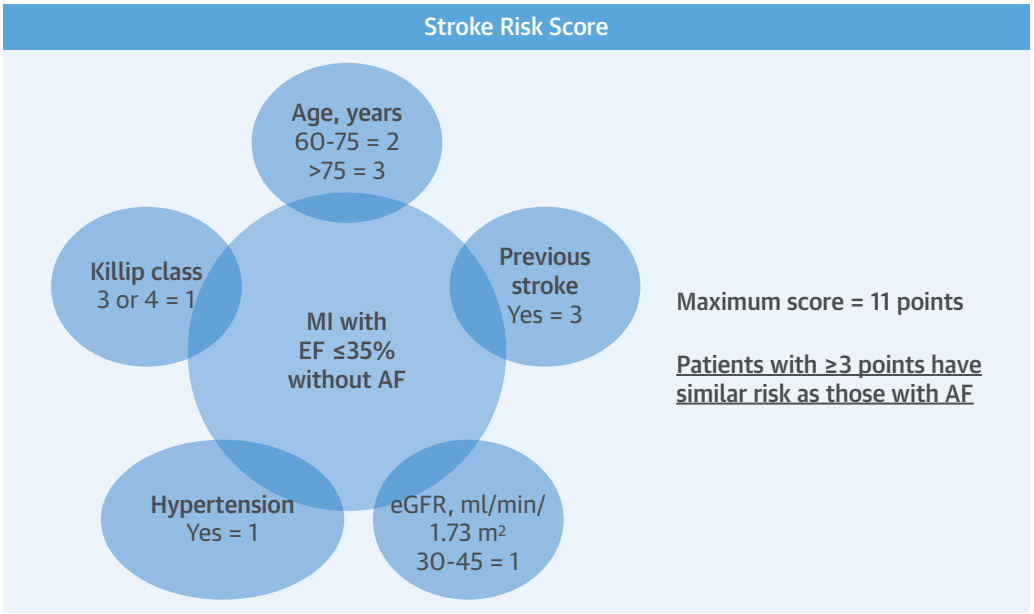
In our study group, the incidence rates for stroke in patients with AF were ≈2-fold higher compared with patients without AF. Patients without AF and with a risk score of 3 or higher had similar (for stroke risk score = 3) or higher (for stroke risk score >3) stroke rates. These data provide an idea of the magnitude of the problem. Patients without AF and with the characteristics depicted herein who have a stroke risk score ≥3 may also benefit from oral anticoagulation, as do their counterparts with AF.

Despite observational data showing that some groups of patients may also be at high risk for stroke despite not having AF (9), oral anticoagulation is not currently recommended as routine strategy for stroke prevention in patients without AF. A strategy of OAC therapy was tested in patients with chronic HF in sinus rhythm (a different setting from that described herein) in the WARCEF (Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction) trial (26). The rate of stroke was similar to that described in our report (≈1.4% at 3 years). As compared with aspirin, warfarin did not reduce the primary composite outcome of ischemic stroke, intracerebral hemorrhage, or death from any cause. However, warfarin was associated with a lower rate of ischemic stroke (0.72 events per 100 patient-years vs. 1.36 per 100 patient-years; $p = 0.005$), but it increased the rate of major hemorrhage (1.78 events per 100 patient-years vs. 0.87; $p < 0.001$), without differences in intracranial hemorrhage rates.

More recently, the COMPASS (Rivaroxaban With or Without Aspirin in Stable Cardiovascular Disease) trial (27) evaluated whether rivaroxaban (2.5 mg twice daily) alone or in combination with aspirin (100 mg once daily) would be more effective than aspirin alone for secondary cardiovascular prevention in patients with stable atherosclerotic vascular disease. Approximatively 62% and 22% of patients presented with a history of MI and HF at baseline, respectively. The primary outcome of cardiovascular death, stroke, or MI occurred in fewer patients in the rivaroxaban plus aspirin group than in the aspirin-alone group (4.1% vs. 5.4%; hazard ratio: 0.76; 95% CI: 0.66 to 0.86; $p < 0.001$), but major bleeding events occurred in more frequently in the rivaroxaban plus aspirin group, without a difference in fatal or intracranial bleeding. The rate of ischemic stroke was lower in the rivaroxaban plus aspirin and rivaroxaban-alone groups compared with the aspirin-alone group, a finding suggesting that low-dose rivaroxaban may prevent the occurrence of stroke even in the absence of AF.

The COMMANDER HF trial (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants With Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) (28) is under way to assess whether rivaroxaban (2.5 mg twice daily) may prevent morbidity and mortality in patients with HF with reduced ejection fraction plus coronary artery disease and without AF. The primary outcome is a composite of death, MI, or stroke. The COMMANDER-HF trial may help to determine whether low-dose rivaroxaban

CENTRAL ILLUSTRATION **Stroke Risk Score for Patients With MI Complicated With Systolic Dysfunction and/or HF**



Ferreira, J.P. et al. J Am Coll Cardiol. 2018;71(7):727–35.

Patients with a score ≥3 have the similar or higher stroke risk compared with patients with atrial fibrillation (AF) in this population.
EF = ejection fraction; eGFR = estimated glomerular filtration rate; HF = heart failure; MI = myocardial infarction.

may prevent stroke in HF patients without AF. Downstream of COMPASS and COMMANDER-HF, whether the score we designed herein may further help identifying an even higher-stroke risk subgroup warrants dedicated testing, along with the effect of antithrombotic strategies in this subgroup.

A particular strength of this study is the validation of our predictive model in another dataset. Consequently, our findings may have clinical implications: with a small number of routinely collected clinical variables it is possible to identify patients with MI (and systolic dysfunction and/or HF) but without AF who are at risk of stroke. Patients with a stroke risk score ≥3 have similar or higher stroke rates than patients with AF. To date there is no trial evidence to justify anticoagulant treatment in these patients, but our findings may help in the identification of patients for such a trial. Of the 5 variables retained in our final stroke risk model, 2 variables were also found in patients with HF with reduced ejection fraction and HF with preserved ejection fraction (9,29,30): older age and previous stroke. However, lower eGFR, hypertension history, and Killip class 3 or 4 are specific to patients with MI with reduced left ventricular ejection fraction.

STUDY LIMITATIONS. First, this was a non-prespecified retrospective study of a pooled dataset from randomized clinical trials. Although the endpoints were independently adjudicated in each trial, no causality can be established, and the associations reported herein are subject to the same potential bias of observational studies. Second, although an electrocardiogram was routinely performed at randomization, we cannot ascertain which patients developed AF after randomization or even which patients had paroxysmal AF without its being reported in the case report form. Hence many patients included in this analysis may actually have AF (or developed AF). The fact that no time interaction was observed may have suggested that this did not have a substantial influence because the risk factors present a short time after MI did not vary significantly across follow-up. Third, the findings reported here cannot be generalized to other patients without these characteristics, particularly post-MI patients with preserved ejection fraction.

Fourth, the type of stroke is not reported in the dataset. We assume that most strokes were ischemic, but hemorrhagic strokes may also have occurred (31). Fifth, there are clinically relevant differences between the derivation cohort (EPHESUS trial) and the other cohorts (OPTIMAAL, CAPRICORN, and VALIANT trials). Differences such as previous HF history (13% in EPHESUS vs. 44% in the other cohorts) and diabetes (32% in EPHESUS vs. 23% in the other cohorts) could have influenced the risk model discrimination. However, the discrimination ability of the developed stroke risk model is similar in validation and derivation cohorts (0.67 vs. 0.66). Sixth, patients without AF but who were treated with OACs were excluded from the present analysis, which was tailored to patients with MI with reduced ejection fraction and without AF or OAC treatment. Moreover, we could not ascertain the reasons for anticoagulation in this study group; reasons could vary widely (e.g., pulmonary embolism, deep venous thrombosis, left ventricular thrombus) and affect the validity of the stroke risk model. Finally, the discrimination of the best stroke risk model developed herein was moderate to good (C-index ≈ 0.7). A higher (>0.7) model discrimination would provide more accurate predictions in discriminating between patients with and without stroke. Nonetheless, a higher discrimination would not change clinical practice. To change or guide patients' treatment, adequately powered, randomized, and controlled evidence is required.

CONCLUSIONS

In a large group of patients with MI complicated by systolic dysfunction or HF but without AF, readily accessible risk factors were identified and incorporated into an easy-to-use risk score. This risk score may help in the identification of patients with a high stroke risk despite their not having AF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among survivors of MI with reduced left ventricular ejection fractions but without AF, those patients with the following clinical features face an increased risk of stroke: advanced age, prior stroke, a history of hypertension, Killip class 3 or 4, and eGFR ≤45 ml/min/1.73 m^2.

TRANSLATIONAL OUTLOOK: These risk factors could be used in future studies to target stroke prevention strategies in patients at greatest risk following MI.

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KEY WORDS heart failure, myocardial infarction, risk score, stroke

APPENDIX For supplemental tables and a stroke risk prediction calculator, please see the online version of this paper.